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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: RONALD J. PETTIS, et al.	Confirmation No.: 7814
Serial No.: 09/606,909	Art Unit: 3763
Filed: June 29, 2000	Examiner: Michael J. Hayes
For: INTRADERMAL DELIVERY OF SUBSTANCES	Attorney Docket No.: 11219-008-999 (500752-999007; P-4901)

SECOND DECLARATION OF DR. RONALD J. PETTIS UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, DR. RONALD J. PETTIS, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application (herein referred to as the '909 application).

2. I am currently a Senior Scientist, at Becton, Dickinson and Company, Inc. which is the assignee of the '909 application.

3. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A.

4. I have been asked to comment on whether intradermal delivery as practiced in accordance with the methods of the invention would always necessarily result in a higher C_{max} and AUC as compared to subcutaneous delivery as recited in the pending claims of the '909 application.

5. As already described in the Declaration I submitted in connection with the '909 application on January 6, 2005 ("the January Declaration"), my co-inventors and I developed an intradermal (ID) drug delivery system that results in an improved pharmacokinetic profile similar to that observed with subcutaneous (SC) delivery, but with enhanced pharmacokinetic parameters. The improved pharmacokinetic profile can be manifested in two or more of the traditionally measured parameters, *e.g.*, faster T_{max} (the time required for the drug to reach a maximum serum concentration), increased C_{max} (the maximum (or peak) serum concentration of the drug reached within a given dose and route of administration), or increased AUC (the area under the serum concentration curve, which is a measure of bioavailability). The embodiment encompassed by the claims currently pending in the '909 application capture one possible pharmacokinetic outcome-- an increased C_{max} and an increased AUC.

6. However, the injection of a drug to the intradermal comapartment does not inevitably result in an increased C_{max} and an increased AUC. Various factors affect the resultant pharmacokinetic parameters, including the particular substance delivered, the rate of delivery used, and the mode of delivery. When a substance is delivered at a varied rate, pressure, volume or depth, a different pharmacokinetic profile may be obtained as evidenced by the data presented below. In particular, when Genotropin™ was delivered to the intradermal compartment as described in ¶ 8 below, the result was a decreased T_{max} and an increased C_{max} as compared to SC delivery, but with a nearly identical AUC. When Almotriptan was administered to the ID compartment as described in ¶ 10 below, the result was a pharmacokinetic profile nearly identical to SC delivery.

7. In a continuation-in-part application of the '909 application (S. Application Serial No. 10/028,988 ("the '988 application"), filed December 28, 2001), Example XI shows that ID delivery of Genotropin™, a recombinant form of human growth hormone, results in

an improved pharmacokinetic profile as compared to administration via the SC route, *i.e.*, an increased C_{max} and a decreased T_{max}, however, the AUC was nearly identical to that observed with SC delivery.

8. In Example XI of the '988 application, Genotropin™ was delivered in a Yucatan mini pig model using a single microneedle. The microneedle had a total exposed length of 1 mm, designed such that the penetration of the needle outlet was limited to 1 mm. Delivery of the The Genotropin™ was controlled using a syringe pump (Harvard PHD 2000, Harvard Apparatus, Holliston, MA) wherein the rate of delivery was 45 μL/min with a delivery duration of 2.2 minutes. The pharmacokinetic profile for intradermal delivery of Genotropin™ was compared directly to that for subcutaneous injection. The pharmacokinetic parameters of intradermal and subcutaneous delivery of Genotropin™ are summarized in Table 2 of the '988 application and is reproduced below, in part, for convenience.

9. It is clear from an inspection of Table 2 that the *pharmacokinetic profile and pharmacokinetic parameters* for Genotropin™ delivered to the intradermal space is improved relative to that of SC delivery -- *i.e.*, demonstrating a decreased T_{max} and an increased C_{max} -- but does not result in a higher AUC. As shown in Table 2, the most striking observations are the more rapid uptake and distribution associated with ID administration. The measured T_{max} for ID delivery is 4-5 fold more rapid than that seen for SC delivery. ID delivery also exhibits a higher C_{max} resulting from more rapid uptake. The uptake and distribution profiles for ID delivery of Genotropin™ more closely resemble IV, rather than SC administration. However, the calculated AUC values for the ID and SC routes are identical.

PK Parameters	SC	ID Single Needle
Dose (IU/kg)	0.161±0.01	0.164±0.01
C_{max} (mIU/L)	158.5±31.0	612.6±187.1
t_{max} (h)	2.75±0.46	0.47±0.25
$AUC_{INF(pred)}$ (mIU x h/L)	920.2±251.7	850.0±170.0

Table 2: Calculated PK parameters for Genotropin™ administration

10. In Example XII of the '988 application, Axert®, Almotriptan malate ("Almotriptan"), was delivered in a Yucatan mini pig model using a microneedle device. The microneedle had a total exposed length of 1 mm, designed such that the penetration of the needle outlet was limited to 1 mm. The Almotriptan delivery was controlled using a syringe pump (Harvard PHD 2000, Harvard Apparatus, Holliston, MA) wherein the rate of delivery was 45 μL/min and 180 μL/min. The delivery duration was 2-2.5 minutes. The pharmacokinetic parameters of intradermal and subcutaneous delivery of Almotriptan are summarized in Table 3 of the '988 application and reproduced below, in part, for convenience.

PK Parameters	SC	ID
C_{max} (ng/mL)	61.0±(19.4)	63.6 (26.1)
t_{max} (h)	0.13(0.05)	0.14(0.08)
AUC	55.9 (6.04)	53.3 (15.7)

Table 3: Almotriptan PK Parameters Following SC and ID Administration

11. It is clear from an inspection of Table 3 that the pharmacokinetic profile and pharmacokinetic parameters of Almotriptan delivered to the intradermal space are similar to SC delivery, but not necessarily enhanced. Indeed, the AUC, C_{max} and T_{max} resulting from intradermal delivery as set out above closely resemble those resulting from SC delivery.

12. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: October 6, 2005

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RONALD J. PETTIS

EDUCATION

1982 - 1986 Georgia Institute of Technology Atlanta, GA
B.S. Chemistry cum laude

1986 - 1988 University of North Carolina Chapel Hill, NC
M.S. Chemistry

1988 - 1991 University of North Carolina Chapel Hill, NC
Ph.D. Chemistry

PROFESSIONAL EXPERIENCE

1996 - Present BD Technologies RTP, NC
Senior Scientist, Team Leader-Therapeutic Drug Delivery
- Wesley J. Howe Award for Corporate Technology Innovation (2001)

1991 - 1996 University of North Carolina, School of Pharmacy Chapel Hill, NC
Research Fellow-Pharmaceutical Formulation and Delivery

PATENTS

6 issued and 17 pending US Patents:

United States Patent 6,722,364 April 20, 2004 *Medicament inhalation delivery devices and methods for using the same*

United States Patent 6,689,100 February 10, 2004 *Microdevice and method of delivering or withdrawing a substance through the skin of an animal*

United States Patent 6,656,147 December 2, 2003 *Method and delivery device for the transdermal administration of a substance*

United States Patent 6,607,513 August 19, 2003 *Device for withdrawing or administering a substance and method of manufacturing a device*

United States Patent 6,595,947 July 22, 2003 *Topical delivery of vaccines*

United States Patent 6,440,096 August 27, 2002 *Microdevice and method of manufacturing a microdevice*

PUBLICATIONS AND PRESENTATIONS

Pettis RJ, Knowles MR, Olivier KN, Kazantseva M, Hickey AJ. *Ionic interaction of amiloride and uridine 5'-triphosphate in nebulizer solutions.* J Pharm Sci. 2004 Sep;93(9):2399-406.

Mikszta JA, Alarcon JB, Brittingham JM, Sutter DE, Pettis RJ, Harvey NG. *Improved genetic immunization via micromechanical disruption of skin-barrier function and targeted epidermal delivery.* Nat Med. 2002 Apr;8(4):415-9.

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Atkins, K.M., Lalor, C.L., Concessio, N.M., Pettis, R.J., Hickey, A.J. (1995) *Aerodynamic size characterization, lung deposition and alveolar macrophage uptake of microparticulate suspension aerosols in guinea pigs, abstract*, 17th Annual Undergraduate Research Seminar, West Virginia University.

Lalor, C.J., Atkins, K.M., Concessio, N.M., Pettis, R.J., Hickey, A.J. (1996) *Lung deposition and alveolar macrophage uptake of microparticulates from suspension aerosols in guinea pigs*, abstract, Society of Toxicology 35th Annual Meeting, Anaheim, CA.

Pettis, R.J., Hickey, A.J. (1996) *Alveolar macrophage activation by muramyl dipeptide aerosols in guinea pigs*: Effects on cellular morphology, poster, AAPS Southeast Regional Meeting, Research Triangle Park, NC.

Pettis, R.J., Hickey, A.J. (1996) Effect of *muramyl dipeptide aerosols on guinea pig alveolar macrophages*, Pharm. Res., 13(9):S166.

Pettis, R.J., Knowles, M.R., Olivier, K.N., Hickey, A.J. (1996) *Ionic interaction of amiloride and uridine-5'-triphosphate (UTP) in solution*, Pharm. Res., 13(9):S179.

Pettis, R.J., Sutter, D., Dekker, J., Bock, R. (2000) *Microfabricated microneedles for disruption of skin barrier function*, poster, 2000 AAPS Annual Meeting and Exposition.

Mikszta, J. Alarcon, J. M. Brittingham, J. P. Dekker, R. J. Pettis, N. G. Harvey *Microdevice-Based Topical Delivery of DNA and Subunit Vaccines.*

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PROFESSIONAL MEMBERSHIPS AND AFFILIATIONS

Member- Controlled Release Society

Member- American Association of Pharmaceutical Sciences

Member-Editorial Board, Drug Delivery Companies Report